γ-Glutamyl Transpeptidase, Triglycerides, and Enzyme Induction

P. J. MARTIN, J. V. MARTIN, D. M. GOLDBERG

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Summary

A study conducted on 109 consecutive patients submitted for routine lipid and lipoprotein screening has shown a significant positive association between serum γ-glutamyl transpeptidase (γ-GT) activity and the serum triglyceride concentration and between serum γ-GT activity and the serum pre-β-lipoprotein concentration. We suggest that these associations may reflect hepatic microsomal enzyme induction in hyperlipidaemic subjects which increases the hepatic content of the rate-limiting enzyme(s) for triglyceride synthesis.

Introduction

During studies of the value of serum levels of γ-glutamyl transpeptidase (γ-GT; EC 2, 3, 2, 1) as an indicator of microsomal enzyme induction an association was observed in some subjects between raised levels of γ-GT and raised triglyceride levels. As the enzymes of hepatic triglyceride synthesis are also located in the microsomes a study was carried out to test whether the relationship was significant.

Subjects and Methods

The screening service for hyperlipidaemia available in the United Sheffield Hospitals provided the source of sera from hyperlipidaemic and non-hyperlipidaemic subjects (referred to here as normal). Patients suffering from chronic alcoholism, liver disease, or a myocardial infarction in the previous six weeks were excluded. None had been regularly receiving barbiturates within four weeks of examination. The primary illness and the lipoprotein classification are given in table I. All patients were instructed to fast overnight; those whose chylomicron level exceeded 0·9 g/l were excluded as their fasting state was in doubt.

TABLE I—*Relationship between Lipoprotein Status and Reason for or Condition Prompting Investigation*

Reason for Presentation	Type IV	Type II b	Type II a	Normal
Hypertension	12	2	3	13
Ischaemic heart disease	8	5	3	10
Other atheromatous disease	8	0	0	9
Endocrine disease	1	5	3	3
Xanthomata	0	1	3	2
Others*	8	1	2	7

* Routine investigation (5), gout (2), non-specific chest pain (3), peripheral neuropathy (1), blurred vision (2), renal calculi (2), pregnant (2), cervical spondylosis (1).

All investigations except nephelometry, which was performed within two days, were completed within a week, sera being stored at 4°C. Triglyceride was estimated by a modification of Soloni's (1971) method, the upper normal limit being 2·26 mmol/l (200 mg/100 ml). Cholesterol was measured on the AutoAnalyzer using Technicon method sheet N24a (upper normal limit 7·77 mmol/l; 300 mg/100 ml). Nephelometry was performed according to Thorp (Stone *et al.*, 1970) using a Scientific Furnishings micronephelometer (upper normal limits 3·25 g and 6·00 g/l for pre-β and β particles respectively). Lipoprotein phenotyping was performed in hyperlipidaemic subjects using agarose gel electrophoresis (Noble, 1968). γ-GT was estimated by the kinetic method of Szasz (1969) but at 37°C instead of 25°C (upper normal limit 30 U/l for males and 22 U/l for females). All statistical procedures were carried out with a Wang Electronics 700C programmable calculator.

Results

Altogether 109 patients were studied, 65 hyperlipidaemic and 44 normal (table I). The distribution of γ-GT activity in the two groups of subjects is shown in fig. 1, and the values for triglyceride plotted against γ-GT activity are shown in fig. 2. Three normal subjects had raised γ-GT levels. One of these was 14 weeks pregnant and had been investigated with negative results for possible insulinoma. The second patient, a 65-year-old woman with hypertension and vertebrobasilar insufficiency, was on thyroxine and methyldopa and had had a hysterectomy seven years previously for postmenopausal bleeding. Apart

TABLE II—*Product Moment Correlation Coefficient (r) for Association between Serum γ-GT Activity and Concentration of Lipid Fractions*

Subjects	Triglyceride	Cholesterol	Pre-β	β
Whole series	0·423*	0·137	0·339*	−0·08
Hyperlipidaemic subjects	0·303†	−0·122	0·254	−0·255

*P<0·001.
†P<0·02.

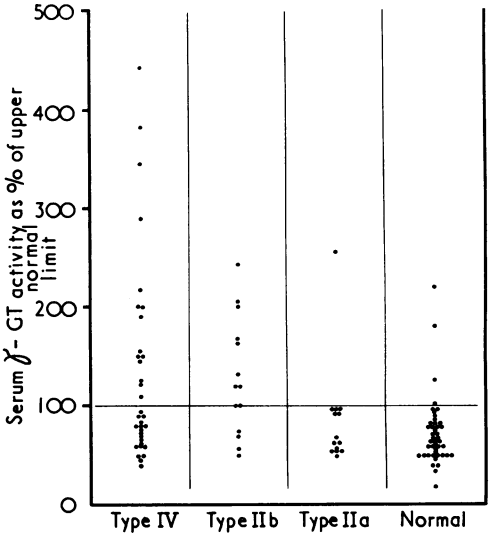

FIG. 1—Distribution of γ-GT activities in normal and hyperlipidaemic subjects.

Department of Chemical Pathology, Royal Hospital, Sheffield S1 3SR
P. J. MARTIN, M.B., M.R.C.PATH., Senior Registrar
J. V. MARTIN, M.B., M.R.C.PATH., Senior Registrar
D. M. GOLDBERG, M.D., F.R.I.C., Consultant

TABLE IV—*Fall in γ-GT Activity and Triglyceride Levels in Three Patients after Treatment*

Case No.	Reason for Investigation	Before Treatment			Treatment	After Treatment		
		Triglyceride (mmol/l)	Cholesterol (mmol/l)	γ-GT (U/l)		Triglyceride (mmol/l)	Cholesterol (mmol/l)	γ-GT (U/l)
1	Family history of I.H.D.	3·51	7·84	40	Diet	1·55	4·37	25
2	I.H.D.	3·72	8·15	37	Diet + clofibrate	1·25	4·99	25
3	I.H.D.	7·34	7·38	36	Diet	2·07	5·18	17

I.H.D. = Ischaemic heart disease.
Conversion: SI to Traditional Units
Triglyceride: 1 mmol/l ≃ 89 mg/100 ml.
Cholesterol: 1 mmol/l ≃ 39 mg/100 ml.

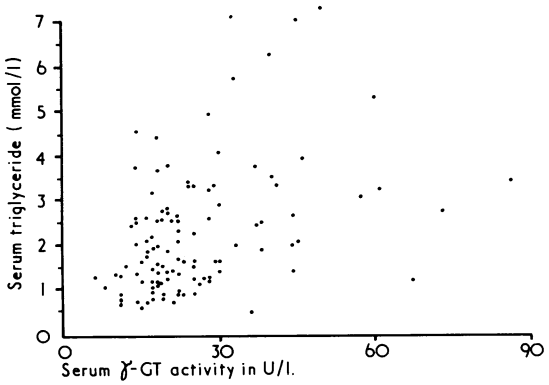

FIG. 2—Relationship between serum triglyceride concentration and γ-GT activity in normal and hyperlipidaemic subjects.
Conversion: SI to Traditional Units—Triglyceride: 1 mmol/l ≃ 89 mg/100 ml.

from a threefold rise in serum alkaline phosphatase activity all her biochemical and immunological values were normal. The third patient was a hypertensive man with a raised serum calcium level, renal stones, and xanthomata.

The correlation coefficients (r) and P values for the association between γ-GT and triglyceride, cholesterol, and pre-β and β-lipoprotein levels in both the hyperlipidaemic subjects and the whole series are shown in table II. The correlation between γ-GT and triglyceride levels in the male subjects was $r=0{\cdot}447$, $n=81$, $P<0{\cdot}001$, and in the female subjects $r=0{\cdot}397$, $n=28$, $P<0{\cdot}05$.

The distribution of increased γ-GT activity according to the presenting illness in the type IV hyperlipidaemic and normal subjects is shown in table III. Abnormal values were distributed

TABLE III—*Proportion of Patients with Increased γ-GT Activity According to Presenting Illness*

Presenting Illness	Type IV Hyperlipidaemia	Normal
Hypertension	4 out of 12	2 out of 13
Ischaemic heart disease	3 out of 8	0 out of 10
Others	4 out of 8	1 out of 7
Other atheromatous disease	4 out of 8	0 out of 9

evenly among the different presenting illnesses in the hyperlipidaemic group. Three patients were investigated before and after treatment. Their results are shown in table IV.

Discussion

The activity of γ-GT has gained prominence as a sensitive index of alcoholism and heavy drinking (Rollason *et al.*, 1972; Rosalki and Rau, 1972) and as an index of liver function (Szczeklik *et al.*, 1961; Rutenberg *et al.*, 1963; Jacobs, 1972). It has been advocated as an index of hepatic microsomal enzyme induction (Idéo *et al.*, 1971; Rosalki *et al.*, 1971; Whitfield *et al.*, 1973) in addition to 6-β-OH-cortisol and D-glucaric acid, the other two commonly used parameters. Alcohol is known to be capable of microsomal enzyme induction. In particular, it induces the microsomal ethanol oxidizing system (Rubin and Lieber, 1971) and probably γ-GT (Idéo *et al.*, 1971; Rosalki and Rau, 1972).

Carbohydrate (in particular, glucose and fructose) even in isocaloric diets has been shown to increase pre-β-lipoprotein and triglyceride levels. There is evidence for this being due to induction of the microsomal enzyme of triglyceride synthesis phosphatidic acid phosphatase, which converts α, β-diglyceride phosphate to α, β-diglyceride in the pathway of triglyceride synthesis (Lamb and Fallon, 1972). It is also of interest to note that induction of the microsomal enzymes of bilirubin conjugation might possibly be caused by carbohydrate. Low-energy diets cause an increase of serum bilirubin in normal subjects and a more marked increase in patients with Gilbert's disease (Owens and Sherlock, 1973).

Enzyme induction by drugs is now a well-recognized phenomenon. In particular, barbiturate and hydantoins are thought to induce the enzymes of bilirubin conjugution, drug metabolism (Whitfield *et al.*, 1973), vitamin D metabolism (Dent *et al.*, 1970), and γ-GT (Idéo *et al.*, 1971; Whitfield *et al.*, 1973). We suggest that the association shown in this paper between raised serum triglyceride levels and increased serum γ-GT activity is due to microsomal enzyme induction, the cause of which could be dietary—for example, sucrose or fructose—in the case of secondary hyperlipoproteinaemias or genetic in the cause of primary hyperlipoproteinaemias. Further studies to test this hypothesis are planned.

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